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14. ABSTRACT

Systemic lupus erythematosus is a potentially deadly systemic autoimmune disease that disproportionately afflicts women and African-Americans. This project is designed to discover genes that increase the risk of lupus in African-Americans. Our goal was to expand the genotyping density in African- Americans (2000 cases and 2000 controls) to increase the number and distribution of genetic markers tested. The genotyping on samples collected in Oklahoma and Birmingham is virtually complete. The control samples from Detroit have had quality and availability issues, which will be addressed in the coming year. At this time genotyping on the OMNI-1s arrays is underway. We have genotyped 2260 subjects on the OMNI-1s single nucleotide polymorphism (SNP) arrays. The quality of the data, in general, has passed our standards. The analysis will begin in year 2 and continue into year 3. The project is proceeding as originally planned.

15. SUBJECT TERMS
Lupus, African-American, Genome Wide Association Study (GWAS), genetic association, genetic susceptibility, candidate gene association study, genotyping

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1. Abstract/Introduction (SF298 requirement)

Systemic lupus erythematosus is a potentially deadly systemic autoimmune disease that disproportionately afflicts women and African-Americans. This project is designed to discover genes that increase the risk of lupus in African-Americans. Our goal was to expand the genotyping density in African-Americans (2000 cases and 2000 controls) to increase the number and distribution of genetic markers tested. The genotyping on samples collected in Oklahoma and Birmingham is virtually complete. The control samples from Detroit have had quality and availability issues, which will be addressed in the coming year. At this time genotyping on the OMNI-1s arrays is underway. We have genotyped 2260 subjects on the OMNI-1s single nucleotide polymorphism (SNP) arrays. The quality of the data, in general, has passed our standards. The analysis will begin in year 2 and continue into year 3. The project is proceeding as originally planned.

2. Body

Since the population history of African ancestry appears to reach back in time much further to the most recent small founder population (~200,000 years) than the other major human ancestries (<50,0000 years for Asian, European, or Amerindian), the extent of linkage disequilibrium is much lower in population samples of African ancestry. This means that the usual approach for finding genetic association using haplotype block tagged markers will be less successful in this ancestry. One way to partially compensate for this problem is to increase marker density, which is what we are funded to do in this project in our genetic study of systemic lupus erythematosus (lupus).

Lupus in African-Americans is more severe and more deadly than in other populations, and especially so compared to European-Americans. Indeed, lupus afflicts women ten times more frequently than men with a strong tendency to strike during the child-bearing years and is relatively common among the Active Duty Military (1).

3. Key Research Accomplishments

Our DOD project is a component of a larger project to more fully characterize African-American genetic association with lupus. Using the other resources we have genotyped 1626 cases and 1572 controls on the OMNI-1 SNP arrays, which provide 1.2 million genetic markers for each subject. Of the 3200 samples genotyped, 1489 cases and 1167 controls satisfied our data quality standards. Data cleaning and preliminary analysis has been completed on these subjects with strong genetic effects found at HLA, IKKB-PLAT1, ITGAM, BANK1, STAT4, IRF5, ATP108/MIR146a, SMO/LOC407835 and SEZ6LFHIT. We are now searching for collaborators with whom to exchange data from controls. This has the potential to double our statistical power, but would require >4000 additional controls.

Meanwhile, genotyping on the OMNI-1s genotyping provides another 1.2 million markers per subject and progresses according to schedule. We have genotyped 1669

cases and 591 controls on this platform. The initial data quality appears to be acceptable, but full data analysis has not been initiated. The DNA from one set of controls from Detroit has issues of quality and availability that we will be addressing in the coming budget year. Otherwise, the plan to genotype as many cases and controls on both the OMNI-1 and OMNI-1s is being executed, following the original specific aims.

4. Reportable Outcomes

1. Anaya JM, Kim-Howard X, Prahalad S, Chernavsky A, Canas C, Rojas-Villarraga A, et al. Evaluation of genetic association between an ITGAM non-synonymous SNP (rs1143679) and multiple autoimmune diseases. Autoimmun Rev. 2011 Aug 5. [Epub ahead of print]
2. Sanchez E, Comeau ME, Freedman BI, Kelly JA, Kaufman KM, Langefeld CD, et al. Identification of novel genetic susceptibility loci in African-American lupus patients using a candidate gene association study. Arthritis Rheum. 2011 Jul 26. doi: 10.1002/art.30563. [Epub ahead of print].
3. Tan W, Sunahori K, Zhao J, Deng Y, Kaufman KM, Kelly JA, et al. Association of PPP2CA polymorphisms with systemic lupus erythematosus susceptibility in multiple ethnic groups. Arthritis Rheum. 2011;63(9):2755-63. PMCID: 3163110.
4. Zhao J, Wu H, Khosravi M, Cui H, Qian X, Kelly JA, et al. Association of genetic variants in complement factor H and factor H-related genes with systemic lupus erythematosus susceptibility. PLoS Genet. 2011;7(5):e1002079. PMCID: 3102741.

5. Conclusions

The planned project to expand the density and number of markers in a case-control study of African-American systemic lupus erythematosus is proceeding as planned.

6. References

1. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, Harley JB. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med. 2003 Oct 16;349(16):1526-33.

7. Appendices

NONE.